REMARKS

Claims 1-21, 37 and 38 presently appear in this case. No claims have been allowed. The official action of January 25, 2008, has now been carefully considered. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method of alleviating the inflammatory response in a subject having an inflammatory condition. This is accomplished by administering to the subject a combination of an anti-inflammatory effective amount of methotrexate (MTX) and an anti-inflammatory effective amount of an agonist of the A_3 adenosine receptor (A_3AR agonist). Unexpectedly, the combination provides a combined anti-inflammatory effect significantly larger than that provided by either MTX or A_3AR agonist used alone.

The examiner has objected to claim 10 for depending on itself.

Claim 10 has now been amended to depend from claim 9, thus correcting this inadvertent typographical error and obviating this objection.

Claims 1-21 have rejected under 35 U.S.C. 112, first paragraph, for lacking enablement for the entire scope of the claim. The examiner states that while the claims are enabling for treating specific types of inflammatory condition or

diseases, such as arthritis or rheumatoid arthritis in a subject, it does not reasonably provide enablement for treating all types or any type of inflammatory diseases or conditions as encompassed by the claims. The examiner states that inflammatory conditions involve various different separate and independent and even unknown pathologies, etiologies or symptoms, and that the treatment of some inflammatory diseases may require more than one distinct separate and independent method and regimen. This rejection is respectfully traversed.

The present claims have now been amended to clarify that they are for treating the inflammatory response in a subject having an inflammatory condition. This language is supported, for example, at page 9, lines 8-10, of the present specification, where it states that the term "anti-inflammatory" denotes the disease modifying effect achieved by the combined treatment "in alleviating the inflammatory response in inflammatory conditions." This inflammatory response is a symptom of the inflammatory condition that is being treated. Thus, applicant makes no claim to being able to cure any disease. Applicant's only claim is that the inflammatory response in the inflammatory condition can be alleviated by means of the present invention. Note that at page 9, lines 17-22, the term "inflammatory condition" is

defined as one that is characterized by a persistent inflammatory response with pathological sequelae. Thus, while the inflammatory condition may have any pathology or etiology, the inflammatory response is expected to be the same and it is this inflammatory response that is being treated. Accordingly, there is no reason to believe that an inflammatory response in colitis, for example, will be substantially different than an inflammatory response in rheumatoid arthritis. Accordingly, particularly in view of the present amendment to the claims, it is no longer unbelievable that the presently claimed treatment will not be applicable to alleviate the inflammatory response in any given inflammatory condition.

Additionally, it is requested that the examiner consider claim 37 in its own right for the purpose of the enablement rejection. New claim 37 has now been added specifying that the inflammatory condition is one in which treatment with MTX is indicated. This language is supported, for example, by the specification at page 9, lines 25-27, where it states:

> However, in accordance with the preferred embodiment, the term "***inflammatory condition***" denotes such conditions in which treatment with MTX is currently indicated.

A number of non-limiting conditions are then specified and these have been presented in new claim 38, which is dependent from claim 37. Accordingly, claim 37, as well as newly amended claim 12, are only directed to conditions treatable by MTX. Furthermore, claim 13 has been amended to specify that the inflammatory condition is one that which is treatable by an A_3AR agonist.

Accordingly, as all of the claims have been amended so as no longer to claim the treatment of inflammatory conditions, but only the alleviation of the inflammatory response in such conditions, and as amended claim 12 and new claim 37 specify that the condition is one in which treatment with MTX is indicated, and claim 13 specifies that the inflammatory condition is one which is treatable by A_3AR agonists, the scope of the present claims is now no broader than the enabling disclosure. Reconsideration and withdrawal of this rejection are therefore respectfully urged.

Claims 1-21 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Jeurissen in view of Fishman. The examiner states that Jeurissen discloses a method of treating a subject having an inflammatory condition (rheumatoid arthritis) by administering an effective amount of MTX, and that Fishman discloses a method of treating an inflammatory arthritis (rheumatoid arthritis) by administering

an A_3AR agonist. The examiner considers it obvious in view of Jeurissen and Fishman to treat rheumatoid arthritis in a subject by administering a composition comprising a combination of MTX and A_3AR agonist, since the combination of compounds that are used to treat the same diseases are well known in the art. The examiner states that it is obvious to combine individual compositions thought to have the same utility to form a new composition for the very same purpose.

Claims 12 and 14-21 have also been rejected under 35 U.S.C. 103(a) as being unpatentable over Fishman in view of Jeurissen. The examiner considers it obvious in view of Fishman and Jeurissen to treat rheumatoid arthritis in a subject by administering to the subject an A_3AR agonist regardless of whether the subjects are being treated with MTX, and especially since Jeurissen discloses that MTX can be used to treat rheumatoid arthritis.

Both of these rejections are hereby respectfully traversed.

The present specification states on page 8, lines 5-9:

> As detailed in the following exemplary embodiment, the invention is based on the finding that treatment of animals having induced inflammatory (Adjuvant induced Arthritis, AIA) with IB-MECA, an A_3AR agonist, in combination with MTX resulted in a combined anti-inflammatory effect,

> significantly larger than any of these drugs alone.

Accordingly, all of the claims have now been amended to specify that the combination of MTX and A_3AR agonist provides a combined anti-inflammatory effect significantly larger than that provided by either MTX or A_3AR agonist used alone. In other words, synergistic results are obtained that would not have been expected by one of ordinary skill in the art familiar with the anti-inflammatory mechanism of action of MTX.

To further explain why the combined effects of the present invention are unobvious and unexpected from any reading of Jeurissen and Fishman, attached hereto is a declaration under 37 C.F.R. 1.132 by Dr. Bruce Cronstein, who is currently Director of the Division of Clinical Pharmacology and is Associate Chairman of Medicine for Research in the NYU Medical Center. In his declaration, Dr. Cronstein explains that, at the time of the present invention, those of ordinary skill in the art would not have expected that an A_3AR agonist would combine with MTX in a manner that would significantly increase the anti-inflammatory effect of MTX alone, and *vice versa*. The declaration establishes that earlier publications by Dr. Cronstein and his colleagues show that the extracellular level of adenosine is significantly elevated

following treatment with MTX, and therefore adenosine is a key mediator in the anti-inflammatory actions of MTX. Since the level of adenosine in the extracellular space is already very high following treatment with MTX, it would not have been expected that an additive anti-inflammatory effect could be obtained with administering to the subject an agonist to adenosine. See particularly, paragraphs 11 and 12 of the Cronstein declaration.

Accordingly, as the present claims now specify that the combination provides a combined anti-inflammatory effect significantly larger than that provided by either MTX and A_3AR agonist used alone, and as the declaration of record establishes that at the time the present application was filed there was no *a priori* reason to expect that the addition of an A_3AR agonist onto the background of an MTX treatment would exert an anti-inflammatory effect beyond that of MTX alone, the present claims only read on results that are unexpected, thereby rebutting any *prima facie* case of obviousness established by the examiner. Reconsideration and withdrawal of these rejections are therefore respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 U.S.C. 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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